

stated. Of the women, one-third were non-smokers, one-third not stated, and the remaining third were moderate smokers." pages 35-36, (4336)

(4350) McNamara; Dubuque, IA

"The rise in the incidence of the bronchogenic lung cancer has been concomitant with the development of the machine age, with the universal use of the gasoline engine, the urbanization of a great proportion of our population, and the prolongation of life through the effective control of many diseases. Therefore, it is evident that more people are exposed to more types of bronchial irritants over longer periods of time than ever before. Because of these facts it is not altogether surprising that bronchogenic carcinoma has increased so notably. Ochsner and DeBakey are convinced that the increased incidence of pulmonary carcinoma is due largely to the increase of smoking, particularly cigaret smoking, which is universally associated with inhalation. All of their patients with the exception of two women were heavy smokers. They published an interesting graph showing the parallel between tobacco production and the incidence of lung cancer per 100,000 population in the country. From the foregoing cursory review it is evident that many theories are held regarding the etiologic factors concerned in the development of bronchial carcinoma. Undoubtedly in most cases there is a combination of factors, including that of heredity." pages 225-226, (4350)

(4353) Murray; Brooklyn, NY

"Aside from the knowledge that some form of chronic irritation plays a leading role in the etiology of these tumors nothing really definite is known. Much speculation has been indulged in but nothing actually proven. Simons reviewed exhaustively all possible etiological factors, pointing out that some form of chronic irritation underlay practically all of them. With slight rearrangement these etiological factors are as follows: 1) Chemical - Inhalation of (a) tar particles, (b) motor exhaust fumes, (c) war gases, (d) tobacco smoke, (e) certain dust (as in pneumoconiosis or in the case of the Schneeberg miners). It is assumed that there has been a marked increase in the above during the past 30 years, coincident with the increase in the incidence of bronchogenic carcinoma." page 391, (4353)

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(4425) Clagett & Brindley; Mayo Clinic, Rochester, MN

"It has been stated many times that the inhalation of radioactive substances will cause the development of carcinoma of the lung. This fact has been demonstrated conclusively by the high incidence of bronchogenic carcinoma in the workers at the Schneeberg radium mines. ... The inhalation of irritating gases, such as exhaust gas from combustion motors and gases arising from tarred roads, has been proposed as a possible cause of pulmonary carcinoma. Many experiments seem to substantiate this belief. However, the incidence of bronchogenic carcinoma reported in those regions where the roads have not changed nor the number of cars increased has increased definitely. After a thorough study of the situation, most investigators of the subject have concluded that the inhalation of tar and benzene products is of little significance in the production of pulmonary carcinoma. ... The opinion frequently has been expressed that the increase in bronchogenic carcinoma may be due to the increase in smoking and the inhalation of smoke." page 840, (4425)

(4533) Holinger, Hara & Hirsch; Hinsdale Sanat., Chicago, IL

"As in all other cancerous lesions in the body, no primary cause is known. Innumerable secondary factors have been suggested and scrutinized. In an exhaustive review of the literature Simons mentions no less than 14 different predisposing causes. These are discussed further by Loizaga. It is generally agreed that no single agent is the sole cause, but that a chronic irritant is an essential common factor. Certain occupations seem to predispose to cancer of the lung. ... Exhaust gases from automobiles and tar on roads have been considered as etiologic factors. Two of our patients, husband and wife travelled extensively from one job to another by automobile. He was a road builder. Both died of bronchogenic carcinoma. Without other corroborative evidence, this, too, must be considered an incidental finding. ... The inhalation of tobacco in smoking is considered by some as a factor causing cancer." (pages 6-7, (4533))

(4554) Muller & Miller; Philadelphia, PA

"Inhalation of light oil derivatives of coal tar and dusts containing silica have likewise been shown to be of etiologic significance in lung cancer. The high incidence of lung cancer in the male sex as compared to

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that of the female sex has been attributed to the use of nicotine, but the recent increase in female smokers has not led to an increase in lung cancer in females." page 42, (4554)

(4615) Clerf & Herbert; Jefferson Hospital, Philadelphia, PA

"Many theories concerning the cause of cancer have been presented. Among these are the occurrence of previous bronchopulmonary disease particularly influenza and inhalation of dusts, exhaust gases from automobiles and particles of tar from road beds. While these may under certain circumstances be considered as predisposing factors there is too little evidence to warrant their serious consideration. Many writers believe that inhalation of tobacco smoke is a responsible factor. Since chronic irritation is generally accepted as a predisposing cause, there should be ample evidence to support the theory that inhalation of tobacco smoke, particularly from cigarettes, is a factor." page 168, (4615)

(4635) Horn; University of Maryland School of Medicine, MD

"The etiology of bronchogenic carcinoma remains obscure. Chronic irritation, bacterial, chemical or physical, persists as a likely or probable contributing factor, despite recent contradictory evidence in the literature. Winternitz predicted an increase in the appearance of the neoplasm following the influenza epidemic of 1918-19. Ewing was firmly convinced that bronchogenic carcinoma occurred more frequently associated with tuberculosis. Macklin and Macklin, in a critical review of the subject of chronic irritation causing carcinoma of the lung, submitted statistical evidence that this hypothesis is unproved and eliminated chronic bronchitis, bronchiectasis, asthma, emphysema, pulmonary abscess, influenza, tuberculosis, and pneumonia as predisposing factors. Inhalation of certain chemicals in the form of dust has become an important consideration in the etiology of lung cancer, particularly in the field of industrial medicine. Karr and Vorwald compiling observations made from roentgenologic, post mortem and experimental studies, concluded that inhaled dusts, except those containing known carcinogenic agents, cannot be considered as causative factors in the development of bronchogenic carcinoma. Holleg and Anguist in a study of 12 cases of carcinoma of the lung in the presence of pulmonary asbestosis reached the same conclusion. The use of tobacco and its

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relation to lung cancer has been a favorite subject of investigation. Ochsner strongly affirms that the rise in bronchogenic carcinoma is caused by the increasing use of tobacco." pages 170-171, (4635)

(4847) Levitt; Harper Hospital, Detroit, MI

"Many investigators have endeavored to establish a connection between bronchogenic carcinoma and chronic irritation of the respiratory tract. Tobacco smoke, air pollution from the exhaust of automobiles, dust raised from tarry roads, have all been suggested as possible causes, but as yet, none of these factors has proven to be the specific cause. Many attempts have also been made to establish a relationship between the occupation and the incidence of carcinoma of the lung. In an exhaustive article on *Occupational Cancer*, Hueper claims, 'It appears that the inhalation of radioactive gases or radioactive dust causes cancer of the lung such as that sustained by miners in Schneeberg and Joachimsthal.' He further adds 'that cancer of the bronchi and lung have been traced to an industrial exposure to arsenicals, chromates, nickel, carbonyl, soot, tar, asbestos and radioactive substances." page 396, (4847)

(4933) Fulton; London, GBR

"There appears to be little difference between the risk run by those employed in indoor as compared with outdoor occupations. In the latter group, labourers and transport workers provide the largest numbers but these groups constitute in any case a fairly high percentage of the outdoor occupation group. Attention might be directed to the apparently high number of cases occurring among furnacemen as a small group, and also among painters. In both of these groups, possible inhalation effects must be considered. While the actual number of cases is too small to justify the drawing of conclusions, the figures point to a possible relationship and appear to warrant a more complete investigation of the incidence of the diseases in these two groups. ... No attempt has been made in this group to analyze the cases in terms of the possible effect of tobacco." pages 777-778, (4933)

(4938) Hayes; Saranac, Lake, NY

"Predisposing Causes. - These are unknown, although excessive smoking of tobacco and, in certain industries, radioactive emanations have been blamed. The increased

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incidence has been parallel in the last four decades to industrial development with its noxious chemicals and gases." page 895, ref. (4938)

Group (c) Articles questioning health hazards of occupational/environmental factors with no mention of tobacco smoke. There was one article that questioned the role of occupational factor in lung cancer patients. The same article also did not mention tobacco smoke. A strict characterization of such articles would essentially be those that favor host susceptibility factors discussed below under Topic E.

(4060) Maher & Saderman; U.S. Navy, PA

"Bronchogenic carcinoma seems to be on the increase. Perhaps more and better diagnostic procedures make this increase more apparent than real. Occupation did not seem to be a factor in our group." page 552, (4060)

Group (d) Articles questioning health hazards of occupational/environmental factors with mention of tobacco smoke. Both articles were by Ochsner and his collaborators. They wrote ten additional articles favoring tobacco smoke as a cause of lung cancer (see above, page 462).

(4164) Ochsner & DeBakey; Ochsner Clinic, New Orleans, LA

"The inhalation of irritating gases, such as war gas, exhaust gas of combustion motors and gases arising from tarred roads, has been suggested as an etiologic factor in the production of pulmonary carcinoma. Kawahata observed 21 cases of carcinoma of the lung in six years among workmen employed in an illuminating gas generator and consequently exposed to dust and hot gases containing tar. Experimentally, it is possible to produce carcinoma of the lung in animals by the use of tar applied to the surface of the animal. Moller painted the backs of young rabbits with tar and observed that a fairly high percentage of the animals had bronchogenic carcinoma. Similar results were observed by Murphy and

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Sturm. Seelig and Benignus found that, whereas only 1 of their control animals had carcinoma of the lung, 8 of 100 mice exposed to coal soot had such lesions. Kumura by means of intrabronchial inhalation of coal tar produced in the lung of a rabbit and a guinea pig small circumscribed nodular neoplasms. Smith observed no pulmonary tumors in 20 mice exposed to coal tar fumes, 1 carcinoma in 26 mice exposed to exhaust of an automobile and 1 pulmonary neoplasm in 29 mice painted with gasoline. He concluded that this proportion was not markedly greater than the spontaneous occurrence of carcinoma of the lung in such animals. Bonne performed experiments on mice by injecting intratracheally dried pulverized tar-acacia emulsion and found no significant increase in pulmonary tumors over control animals. Similarly, Campbell concluded that exposure of mice to exhaust gas from internal combustion engines has little effect on the incidence of primary tumors of the lung as compared with that among controls. Hampeln stated the belief that there is a definite relation to the increased production of smoke and dust in large cities, in that these substances by constant inhalations produce a chronic irritation of the bronchial and pulmonary epithelium, increasing the frequency of carcinoma of the lung. Staehelin also stated the opinion that the belief that the small tar and dust particles in the dust of tarred or oiled roads and the oxidation of products of gasoline and benzene inhaled daily in large amounts are causative factors for the increase. An increased incidence in carcinoma of the lung among open air workers exposed to road dusts was observed by Kennaway and Kennaway. Heilman also stated the opinion that the inhalation of gasoline and tar products originating from the use of automobiles and tarred roads is responsible for the production of pulmonary carcinoma. On the other hand, Davidoff and Uspensky stated that in Russia, where there are few automobiles and few, if any, of the roads are painted with tar, there has been a definite increase in carcinoma of the lung in the past ten years. Similar observations have been made by Boyd in Canada and by Husted and Billman in Denmark. Passey and Holmes contended that in Great Britain the increasing incidence in pulmonary malignant tumor began before the tarring of roads. Similarly, Konrad and Franke observed that the condition is increasing in the town of Riga, where there has been no increase in the tarring of roads or in the number of motor cars. As a result of his investigations of the tar content of dust raised from tarred streets by motor vehicles, Lehmann concluded that this factor is of little etiologic significance.

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Probst made a thorough review of this subject and came to a similar conclusion. **These facts would certainly tend to disprove the importance of the inhalation of tar and benzene products in the production of pulmonary carcinoma.**" pages 216-217, (4164)

(4555) Ochsner, Dixon & DeBakey; Ochsner Clinic, New Orleans, LA

"An apparently plausible theory concerning the cause of bronchiogenic carcinoma is inhalation of irritating gases such as exhaust gas of combustion motors and gases emanating from tarred roads. Kawahata observed 21 cases of carcinoma of the lung in six years among workmen employed in an illuminating gas generator and consequently exposed to dust and hot gases containing tar. Hampeln stated the belief that there is a definite relation to the increased production of smoke and dust in large cities in that these substances by constant inhalation produce a chronic irritation of the bronchial and pulmonary epithelium, increasing the frequency of carcinoma of the lung. Staehelin also stated the opinion that the inhalation of dust containing chemical substances which possess a specific carcinogenic agent is responsible for pulmonary carcinoma. An increased incidence of carcinoma of the lung among open air workers exposed to road dusts was observed by Kennaway and Kennaway. This is not substantiated by our experience because in our 58 patients subjected to pneumonectomy, 32 (55.2%) had indoor occupations and 26 (44.8%) worked out of doors." pages 1197-1198, (4555)

As stated above (page 468), DeBakey and his collaborators reversed their opinion on the primary importance of cigarette smoking as a cause of lung cancer. However, they did not alter their opinion on the questionable role of occupational/ environmental factors prior to 1950.

Human Studies on Industrial Pollutants

This subsection is devoted entirely to results of original studies on population groups for cancer incidence of lung, skin and liver. It is important to separate concepts evolving from

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human studies and animal experiments. Among original studies listed below, the most important one that was repeatedly discussed through the 1950's and 1960's was entitled *Health Costs of Urban Air Pollution* by Mills and Mills-Porter (4862) and is selected as a highlight publication. Their articles listed below appeared prior to 1950; during the 1950's, both authors discussed additional role of cigarette smoking (see Chapter V). Harris did not mention articles listed during the 1940's and cited only those for the 1950's in his SOA report.

Mills wrote a historical review of the importance of urban pollution:

"The industrial Revolution and modern machinery have wrought great changes in human existence. Many of these changes have been toward a higher type of life, but such blessings have not been un-mixed with evil. Growth of large metropolitan centers of great population density, and the use of enormous tonnages of coal for heat and power, have created certain hazards to health the true seriousness of which are finally coming to be realized. Quite aside from the social and economic aspects of city slums, the pollution of their atmosphere poses health problems quite as serious as those which were relieved by water purification plants a half century ago. Close analysis of the health damage wrought by such air pollution provides an ample basis for smoke clearance campaigns entirely aside from any probable reduction in laundry bills, painting and redecorating costs, etc. The average person takes two to three quarts of food and drink in through his mouth each day, but in the same time he takes into his lungs 10 to 20 thousand quarts of whatever atmosphere happens to be around him. Most of the dirt or pollution in this large volume of inspired air is caught and held in his respiratory system. Early in the present century Ascher pointed out the increased respiratory disease hazards faced by people living in atmospheres polluted by coal smoke. He found the pneumonia mortality 135 per cent higher in men of the Ruhr valley than in Prussian men of similar age groups, with the death rate highest in the

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industrialized areas of worst pollution. Pneumonia caused 6 times more nursing deaths in industrial than in rural populations. Ascher also found that coal smoke quickened tuberculosis deaths in laboratory animals and increased their susceptibility to aspergillus pneumonia. The damaging effect on people was greatest in those industrial areas where humidity was high and fogs prevalent. In 1912 White and Marcy presented data showing a close relationship between sootfall and pneumonia death rates in the 27 wards of Pittsburgh; with tuberculosis the relationship was less regular but still significant. They used only total mortality data, making no breakdown by sex or color. In 1938 Haythorn and Meller found that it concerned Pittsburgh men much more than women, for the male death rate from pneumonia was 50 to 90 per cent higher than the female in each year studied (1927-1936). They offered no explanation for this higher male rate. Necropsy findings of more marked anthracosis in lungs where healing had been by organization of unresolved pneumonia was suggested by them as probably due to a clogging of lung lymphatics with carbon particles." page 496, (4551)

Urban air pollution. Mills & Mills-Porter from the Laboratories for Experimental Medicine of the University of Cincinnati, wrote an article on this subject. In a study of death rates due to respiratory disease, Mills reported that incidence for respiratory tract cancer was higher in "dirtier industrial areas of Cincinnati and Pittsburgh, than in cleaner residential suburbs." The high rates for pneumonia and tuberculosis in slum areas have been attributed by other investigators to poor housing, overcrowding and poor nutrition. However, since male death rates were higher than women, Mills raised some doubt that these economic factors provided the whole answer.

In a later study, Mills & Mills-Porter added surveys for Chicago, Detroit, Nashville and Atlanta, and resurveyed Cincinnati (4862). Their conclusions were as follows:

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"Death rates for pneumonia, pulmonary tuberculosis and respiratory tract cancer bear a direct and significant relationship to the intensity of pollution in urban atmospheres. Males are involved much more than females in these effects of pollution. In Chicago, where large population numbers give stable results, the rise in death rates from pneumonia and tuberculosis from clean to dirty districts is ten times greater for males than for females, and the rise in death rates for buccal and respiratory tract cancer is more than four times greater. Based on the low rates prevailing in its clean suburbs, Chicago each year has an excess of 258 deaths from pneumonia among white males in its dirtier districts, 241 from tuberculosis and 69 from buccal and respiratory tract cancers - a total of 568 deaths among white males each year from these three respiratory diseases alone in excess of the death rates these diseases show in the city's cleanest districts. Add to this one-tenth as many deaths for white females and for Negro males, and a grand total is obtained of roughly 700 deaths each year, which represents a measure of the respiratory hazard of living in Chicago's dirtier districts. The observation that death rates from buccal and respiratory tract cancers rise along with those from pneumonia and tuberculosis points strongly to a general irritation of the tract as the basic factor involved. Economic, housing and nutritional factors appear of much less importance than air pollution, as evidenced by the difference between hazards to males and females." page 633, (4862)

Mills and Mills-Porter further discussed the potential role of cigarette smoking:

"The tenfold difference in excess deaths between males and females in dirty districts seems much more than could be accounted for on the basis of more daily hours of exposure in the dirty air for the men. One would be inclined to look elsewhere for a factor which is working synergistically with the outdoor air pollution to affect the respiratory tracts of men in particular. One at once thinks of tobacco smoke in this connection for the percentage of men who smoke is almost three times as great as that of women. In an article soon to be published, we shall show that tobacco smoking is significantly related to buccal and respiratory tract cancer and pulmonary tuberculosis, while Morton recently reported postoperative pulmonary complications six times more prevalent in patients who were habitual smokers

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before operation than in nonsmokers. It is therefore quite possible that the really alarming respiratory hazard men face in urban areas of heavy air pollution may be due to the combined and cumulative effects of such pollution in conjunction with the chronic irritational action of tobacco smoke. In cleaner suburban or rural areas, the respiratory hazard is only slightly greater for men than for women; women (with a low percentage of tobacco smokers) are less affected by the air pollution hazard. Hence we must consider the likelihood that the male hazard results from the combined effects of coal smoke and tobacco smoke." page 631, (4862)

The authors proceeded to discuss outdoor air pollution that continue to apply through the 1980's when a new Clean Air Act is under consideration:

"The needed steps for lessening outdoor urban air pollution have already been discussed. Widespread change to diesel power for railroad switching and long haul purposes has brought great improvement except in cities near the sources of high volatile coal, such as Cincinnati, Birmingham, Ala., Nashville, Tenn., and Louisville, Ky. These cities will get relief only through compulsory dieselization. Compulsory use of low volatile coal in hand-fired heating equipment has been shown to provide the best solution to smoke production in the home, but the increased demand for the limited supplies of low volatile coal bid fair to bring about a considerable price boost. Methods of processing high volatile coals for smokeless combustion are now receiving intensive study, so great relief from the carbon factor in air pollution may be expected. Fly ash and industrial dusts or wastes still pose a difficult problem, however, one on which St. Louis is now busily concentrating her attention after her remarkable victory over the carbon and sulfur oxide factors." page 632, (4862)

Incidence of lung cancer in six cities. Dorn, a senior economist at the U.S. Public Health Service, examined the number of new cases reported in 1938 to 1940 from six cities: Philadelphia, Alameda and San Francisco, Chicago, Detroit,

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Pittsburgh and Denver. Dorn discussed the role of air pollution as follows:

"Although exact measures of the air pollution are not available, it is generally thought that, of the cities listed in table 4, the greatest amount of pollution is in Pittsburgh. However, the incidence rate for lung and respiratory cancer in males is lower in Pittsburgh than in any of the other cities except Denver. There is less difference in the rates for females; in fact these data indicate that there is no real difference in the rates of the surveyed cities. These data do not necessarily prove that atmospheric pollution has no effect upon the incidence of respiratory cancer. On the other hand they offer no affirmative evidence that such is the case. The causes of respiratory cancer are probably too complicated to be discovered in this relatively crude manner." pages 1270-1271, (4330)

Occupation and incidence of lung cancer. Kennaway & Kennaway (4759) extended the statistical analysis of death certificates for lung cancer in males from England and Wales. Their earlier publication covered deaths reported from 1921 to 1932 (see Chapter III, page 265) and their later one that extended coverage to 1938, is selected as a highlight publication. The conclusions of the Kennaways apply only to England and not to the United States, because of differences in fossil fuel consumption:

"(1) The death certificates for cancer of the lung and of the larynx in males from England and Wales for the years 1921-38 inclusive numbering 38,418 have been investigated and the periods 1921-32, 1933-38 are compared. The 63 occupations examined employ about 30 per cent of the male population aged 20 and upwards. (2) Sources of error in statistical work on death certificates are discussed. (3) The increase in the recorded cases of lung cancer cannot be attributed to any increase of data obtained by autopsy. (4) The agricultural and coal-mining industries show a low

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incidence of cancer of the lung and of the larynx. (5) A group of open-air occupations where there is exposure to the dust of roads has ratios above 100 for cancer of the lung and of the larynx with the exception that motor drivers have a normal liability to cancer of the larynx. But the comparative incidence of cancer of the lung is not increasing distinctly in any of these occupations and in the pavers, street masons, concretors and asphalters there has been a distinct fall in the ratio. (6) The occupations in which there is a liability to silicosis do not show a high incidence of cancer of the lung, but there are in the literature some studies of small numbers of cases in which the two conditions were asso-ciated. (7) Cases of cancer of the lung have occurred in some occupations involving exposure to asbestos. (8) In the death certificates examined and in the Reports of the Chief Inspector of Factories, no occupations involv-ing exposure to any kind of dust except those concerned with asbestos, arsenic and nickel which employ very small numbers have been found in which there might be an increased incidence of cancer of the lung. (9) Workers exposed to coal gas and tar tend to show an increased prevalence of cancer of the lung but in the later period studied the incidence does not exceed two and a half times that on the general population. (10) Occupations concerned with the supply of alcohol have a high incidence of cancer of the larynx. (11) The later period studied shows a considerable decrease in the occurrence of cancer of the lung in those engaged in the preparation and sale of tobacco. (12) The very moderate ratio (125) for cancer of the lung in medical men is important in regard to the view that the recent rapid increase in recorded deaths from cancer of the lung is due to the detection of more cases by improved diagnosis, for this is an occupation where the availability of the existing methods for the detection of cancer is presumably at a maximum. (13) No special occupations have been found, among the 63 examined, to which the increase in the total of cases of cancer of the lung can be attributed. This increase is now so great that the incidence upon any such occupations would have to be very high indeed. (14) No evidence has been found that tarring of roads has affected the incidence of cancer of the lung. Such data as are available suggest that coal tar in the atmosphere, whether derived from roads, domestic chimneys or any other source, does not cause an exceptionally high incidence of cancer of the lung. Cotton mule spinners show an especially high incidence of cancer of the lung, although they inhale air sprayed with an oil which

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produces cancer of the skin. Much further work is required on the factors which regulate the penetration of particles and droplets of various shapes and sizes into the air passages. (15) The higher mortality from cancer of the lung in towns, the low mortality in agricultural occupations, and the absence of social gradient are compatible with an etiological factor in the air such as coal smoke. But in any comparison of urban and rural areas, the question of facilities for diagnosis must be considered. (16) Soot is probably a decreasing contaminant of the air owing to the substitution of other sources of heat for the domestic fire, which is the chief source of soot-containing smoke. Hence coal smoke does not account well for any recent increase in cancer of the lung. Among various possible factors which have been suggested to account for the increase is tobacco smoke; the consumption of tobacco has risen, and so has the percentage of it smoked in the form of cigarettes of which the smoke is often inhaled: such an effect of tobacco would accord well with the absence of social gradient." pages 296-297, (4759)

The role of tobacco smoke in lung cancer patients was discussed by the Kennaways:

A possible connection between tobacco, and especially cigarettes, and cancer of the lung, has been suggested many times, perhaps most recently in the case of Turkey. Peacock has pointed out that cancer of the stomach is far more common in man than, so far as we know, in any other species and has suggested that this is due to his use of heated foods. A similar argument might be applied in the case of cancer of the lung, which is not known to be prevalent in any of the lower animals. The adenoma of the lung of the mouse, and certain affections of the lung of sheep in South Africa and Iceland, are neoplasms of which the exact nature is uncertain. We know one instance at any rate of the susceptibility of the lung of an animal to a carcinogenic agent namely the lung of the cat in relation to 2-acetylaminofluorene given by the mouth: hence there is no reason to think that animals are immune to any such agents. One obvious factor, possibly carcinogenic, to which the lung of man alone is exposed is tobacco smoke. During the present century very considerable changes have taken place in this country in the social distribution of the various method of smoking. There were of course exceptions to any rule, but roughly one might say

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that in the earlier part of this period men of the richer classes smoked pipes, cigarettes and cigars, and men of the poorer classes smoked pipes: cigarette smoking was increasing among the richer women, while women of the poorer classes did not smoke. One never saw a women scrubbing her front door-step or hanging out the washing, with a cigarette in her mouth. The great change which has taken place in the later years is the general increase of cigarette smoking and its adoption by women of classes which formerly did not smoke at all. Men in occupations which do not subject them to any restrictions in this matter, e.g. builders, workmen, painters, window cleaners, dustmen and road sweepers, who used to smoke a pipe at meal times, now smoke cigarettes while at work. Cigarette smokers are said to inhale more than do smokers of pipes, but it is very difficult to get any conclusive evidence upon this matter, which might be important. There is some American literature, which has been summarized upon the arsenic content of tobacco and tobacco smoke. The occurrence of cancer of the lung in makers of arsenical sheep-dip indicates the impossible importance of this factor. Some writers have contended that smoking cannot be associated with cancer of the lung because this form of cancer has increased more among men, while the use of tobacco has increased more among women. But the sexual distribution of cancer involves unknown factors and does not provide a very secure basis for an argument of this kind. Of course no claim is made here that the simultaneous increases in the consumption of tobacco, and in cancer of the lung, proves any etiological connection between the two. Other changes which have taken place in the same period, which no one proposes to associate with cancer of the lung, e.g. the increase in the issue of wireless licenses show a very similar curve, and such correlations are a common subject for statistical witticisms. Thus wireless licenses have increased at a rate (about 10-fold in the last 20 years) similar to that shown by deaths from cancer of the lung, or from coronary disease. The annual consumption of tobacco in the United Kingdom has increased from 128 million pounds in 1924 to 250 million pounds in 1946, and the percentage of these amounts smoked in the form of cigarettes has risen from 56 in 1924 to over 80 in 1943-5. Thus the consumption of cigarettes shows a considerable increase both absolute and relative." pages 293-295, (4759)

Additional publications on causation of lung cancer. Farber & Edwards, from the San Francisco Department of Public Health,

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reviewed the medical history of 50 cases of primary lung carcinoma. They reported that in 16 individuals (32%) there was an exposure to dust or other irritating substances (4524). Moshman and Holland reviewed the age standardized rate of cancer among Oak Ridge employees and their resident dependents. The lung cancer rates in white males was proportionately higher than national average which could not be explained because of lack of information on personal habits and socio-economic conditions (4954). In an editorial entitled "Aetiology of Lung Cancer" appearing in the British Medical Journal, the following sentence appeared: "Tar, certain lubricating oils, soot, arsenic and various radioactive substances will cause epithelioma of the skin; the long continued inhalation of any such substance may well produce cancer of the lung." (4331). The editorial opinion emphasized the lack of inhalation studies relevant to lung cancer in contrast to numerous animal skin experiments relevant to human skin cancer.

Occupation and skin cancer. A monograph entitled *Cancer of the Scrotum in Relation to Occupation* was written by Henry, formerly H. M. Medical Inspector of Factories (4601). He also wrote a comprehensive review article entitled *Occupational Cutaneous Cancer Attributable to Certain Chemicals in Industry*. It is important to recognize that the chemicals in coal tar products were also being tested in animals and shown to cause skin cancer. Henry and his colleagues did not support the

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suggestion that studies on coal tar applied to skin are relevant to pulmonary carcinogenesis associated with cigarette smoking. Other publications on skin lesions due to pitch and tar did not suggest that tobacco tar could likewise cause lung cancer (4727) (4781) (4879).

Experimental Dermal Carcinogenesis

During the 1940's, there was an intensive testing of polycyclic aromatic compounds on formation of skin cancer in experimental animals, preferentially mice. I have collected over 60 articles from scientists in the United States, Great Britain and other countries. It is important to emphasize that there were no statements relating to application of results of dermal carcinogenesis to cigarette smoking and lung cancer. The exceptions to this general rule are mentioned below and relate to the occurrence of benzpyrene in coal tar and tobacco tar.

Pathology of tumours. This was the title for the monograph written by Willis (from the Royal College of Surgeon, London) and a highlight publication for the 1940's. The chapter on *Experimental Production of Tumours* included the background for searching carcinogenic agents in tars and oils (4802):

"Since tars and oils are highly complex mixtures of substances, and since different tars and oils were found to vary markedly in their carcinogenic efficacy, it soon became evident that a search must be made for specific ingredients responsible for carcinogenesis. Many workers cited by Woglom investigated the relative efficacy of tars of different kinds, of different tar-fractions obtained by distillation, and of tar extracts

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made with solvents. Notable amongst these was J. A. Murray who prepared a highly carcinogenic ethereal extract of tar. But by far the most important of the researches into the chemistry of carcinogenic tars were those of Kennaway and his collaborators from 1923 onwards, the main results of which were outlined by Kennaway in 1930. These showed that the carcinogenic factor in tar was present in the higher-boiling fractions; that potent carcinogenic tars could be made artificially by heating acetylene, isoprene, skin, yeast, cholesterol or human skin or voluntary muscle to temperatures between 700° and $920^{\circ}\text{C}.$; and that a non-carcinogenic petroleum could be made carcinogenic by heating to $800^{\circ}\text{C}.$, in the process of which aromatic hydrocarbons are formed from those of the aliphatic series. Twort and Fulton prepared highly active tars by heating turpentine and pinene. In 1930 Mayneord and Hieger, working with Kennaway, made the important observation that the fluorescence spectra of many cancer producing mixtures, including gas-tar, acetylene-tar, yeast-tar, muscle-tar, cholesterol-tar, ethereal extract of gas-tar, pitch distillate, heated petroleum and shale oil, showed the same bands at wave-lengths 4,000, 4,180, 4,400 Å. These bands were like those of the fluorescence spectrum of the polycyclic hydrocarbon 1:2-benzanthracene. Accordingly, Kennaway made a special study of hydrocarbons allied to 1:2-benzanthracene, and found 1:2:5:6-dibenzanthracene to be carcinogenic. At last a chemically pure carcinogenic compound had been identified, not indeed as a constituent of tar, but as a result of painstaking studies of the physical and chemical characters of carcinogenic tars. Kennaway was careful to point out that 'neither benzanthracene nor any of its derivatives have been found and perhaps have not been sought for, in coal tar', and to suggest prophetically that among the many compounds still undiscovered in tar some might be found 'far more powerfully carcinogenic than any known substances'. So also Hieger, in discussing the significance of the discovery of characteristic bands in the spectra of carcinogenic mixtures, insisted that 'the substance responsible for the bands may not be identical with the cancer-producer but is some closely allied compound ... The carcinogenic agent in tars and oils may be only one of a group of such compounds'. The value of the fluorescence test was, in Hieger's own words, 'to indicate the probability of carcinogenic activity and to assist in directing the preparation of appropriate hydrocarbons'." pages 31-33, (4802)

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Willis summarized five groups of carcinogenic hydrocarbons that were tested in pure form on experimental mice, as follows:

"The importance of the discovery of pure carcinogenic hydrocarbons by the London workers can scarcely be exaggerated. It gave a tremendous impetus to both chemical and biological work in this field. Many new carcinogenic compounds have been produced, and tar-cancer research has largely been superseded by more precise researches with these chemically pure substances. The number of such substances now runs into scores, and only the most important can be mentioned here. For more detailed accounts, consult the papers of Kennaway and his co-workers already cited, and those of Fieser and Shear.

(a) Simple derivatives of 1:2-benzanthracene. This substance, 1:2-benzanthracene itself is only very feebly carcinogenic, but many of its simple substitution derivatives are much more active. This applies particularly to derivatives containing substitution groups at the position 10, 5, 9 and 6 of the benzanthracene complex. Thus 10-methyl-1:2-benzanthracene, 5-methyl-1:2-benzanthracene, 9-methyl-a:2-benzanthracene, and 6-methyl-a:2-benzanthracene have all been prepared synthetically and shown to be active carcinogens, in that order of decreasing potency. Further, if suitable simple substituents are introduced into two of these favourable positions, they then reinforce each other, giving a highly potent carcinogenic compound. This applies to the 5:6, 5:9, 5:10 and 9:10 dimethyl derivatives. The last-named is the most active carcinogenic hydrocarbon so far discovered; with it, Bradbury and co-workers obtained skin cancers in mice as early as the 32nd day after the initial application.

(b) Methylcholanthrene and cholanthrene. These merits special interest, not only because the former is second only to 9:10-dimethyl-1:2-benzanthracene in carcinogenic activity, but also because the cholanthrenes are closely related chemically to the bile acids. Thus methyl-cholanthrene has been prepared from both deoxycholic acid and cholic acid; and both it and the parent hydrocarbon cholanthrene have also been synthesized. Ethylcholanthrene has also been prepared and shown to be an active carcinogen. From the structural formulae it will be seen that these compounds again are really 1:2-benzanthracene derivatives with substituents in the carcinogenically favourable positions 10, 5 and 6; methylcholanthrene being particularly notable in that all three of these positions carry substituents.

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(c) 3:4-benzpyrene. This is certainly the most active and perhaps the only important, carcinogenic constituent of coal tar. It was first isolated from coal-tar pitch, and later prepared synthetically. In accord with Kennaway's 1924 work, the highest boiling fractions of tar contain relatively large amounts of benzpyrene; and the fluorescence spectrum of benzpyrene is of the same type as that of 1:2-benzanthracene. Its close relationship to this substance is evident from its structural formula, which shows that it is really a benzanthrane derivative with an additional benzene ring affecting position 9, where we have already seen substitution is favourable for the development of carcinogenic properties. Benzpyrene is only slightly inferior to methylcholanthrene in potency. Some of its simpler derivatives are also carcinogenic, though less powerfully so than the parent hydrocarbon. A high order of carcinogenic activity is shown also by three hexacyclic dibenzpyrene which have been prepared.

(d) 1:2:5:6-dibenzanthracene. This is notable as being the first pure hydrocarbon to be shown to be carcinogenic; and since the discovery of this substance, it has been widely used by research workers. It is capable of producing tumours in a high proportion of mice, but it does so relatively slowly. In molecular structure it also is a 1:2-benzanthracene derivative with an added benzene ring as a substituent at positions 5 and 6.

(e) Some other carcinogenic hydrocarbons and related compounds. Certain other hydrocarbons and certain heterocyclic nitrogen-containing compounds with structures analogous to the carcinogenic hydrocarbons of benzanthrane type have also been shown to be feebly carcinogenic. These include 1:2:5:6-dibenzfluorene, 1:2:5:6-dibenzacridine, 3:4:5:6-dibenzacridine, 1:2:5:6-dibenzcarbazole and 3:4:5:6-dibenzcarbazole. The ways in which these compounds resemble and differ from the benzanthrane derivatives in molecular structure are shown in Table I. Dibenzcarbazole also produces liver tumours in painted or injected mice. It is of interest to find that 3:4-benzphenanthrene and 2-methyl-3:4-benz-anthrane, which are unrelated to benzanthrane, have considerable carcinogenic potency. Morton et al also claimed that triphenylbenzene and tetraphenylmethane were carcinogenic, but Cook and Kennaway, Shear and others have been unable to confirm this. The discovery of Kennaway and co-workers, referred to by Badger et al., that under certain conditions deoxycholic acid, a normal component of bile,

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can induce sarcomas in mice, is a remarkable one and may prove of far-reaching importance." pages 33-34, (4802)

Finally, Willis reviewed the relative potency of carcinogenic hydrocarbons. The order of potency from highest to lowest was as follows: 9:10-dimethyl derivative of benzanthrane, methylcholanthrene, benzpyrene, dibenzanthracene, and dibenzacridine.

National Cancer Institute. The scientists from this Institute supported by the U.S. government, and their field of research relating to dermal and pulmonary carcinogenesis following administration of polynuclear aromatic hydrocarbons, were as follows:

(4020) Andervont: susceptibility of hybrid mice to pulmonary tumors induced by subcutaneous injection of methylcholanthrene.

(4021) Andervont & Shimkin: pulmonary tumors in mice induced after intravenous or subcutaneous compounds such as 3:4-benzpyrene and 20-methylcholanthrene.

(4039) Grady & Stewart: pulmonary tumors induced in strain A mice by subcutaneous injection of 1,2,5,6-dibenzanthracene or methylcholanthrene.

(4040) Grady & Stewart: pulmonary tumors arising from alveolar cells began to appear 5 weeks after subcutaneous injection.

(4083) Shimkin: susceptibility of seven strains of mice to pulmonary tumors induced by intravenous injection of methylcholanthrene.

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(4084) Shimkin: continuation of induction of pulmonary tumors in mice; the substances which have been found to produce pulmonary tumors in mice include tar, probably owing to its content of the three common polynuclear aromatic hydrocarbons: methylcholanthrene, dibenzanthracene and benzpyrene.

(4085) Shimkin & Andervont: relative potency based on latent time or carcinogenic index of methylcholanthrene, benzpyrene and dibenzanthracene.

(4086) Shimkin & Letter: The Discussion and Summary are important because they include significance of animal experiments to human lung cancer and air pollution. This article is the only highlight publication under the subtopic of experimental carcinogenesis of polynuclear aromatic hydrocarbons conducted by American scientists:

"The incidence and the number of primary pulmonary tumors in mice of susceptible strains can be increased by the introduction into the animal of carcinogenic hydrocarbons and related compounds. The susceptibility of the mice to induced pulmonary tumors is parallel to their susceptibility to spontaneous tumors of the lung, i.e., strains which are most susceptible to their spontaneous occurrence are most susceptible to their induction with carcinogens. The carcinogenic chemicals can be injected by various routes, including the intra-tracheal, in order to elicit the neoplastic response in the lungs. Experiments conducted at this laboratory suggest that the increase in the number of pulmonary tumors in mice exposed to certain dusts is not owing to nonspecific irritation but to the presence of some carcinogenic material in the dust. Campbell obtained the highest incidence of pulmonary tumors in mice exposed to dust from tarred roads. It is known then some coal tars contain a powerful carcinogenic agent, 3,4-benzpyrene. The increase in the incidence reported with dust which had been extracted with benzene was not so impressive, and no indication concerning the

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completeness of the extraction was given. Contrary to Campbell's postulation that nonspecific irritation plays a part in the genesis of pulmonary tumors in mice, the experiments reported here fail to indicate that nonspecific irritation produces pulmonary tumors in mice or aids in their induction with carcinogens. It is also significant that the development of pulmonary tumors in mice of strain A injected subcutaneously or intravenously with 1,2,5,6-dibenzanthracene or 20-methylcholanthrene is not associated with any demonstrable inflammatory reaction. One of the possibilities given in explanation of the increase in the pulmonary tumors in mice painted with tar is that the procedure in some ways alters the physical state of the animal so that its resistance to carcinogenesis is lowered, and pulmonary tumors arise at points of incidental irritation of inhaled dust particles. Mice born and raised in an atmosphere practically devoid of dust are just as susceptible to the induction of pulmonary tumors after the subcutaneous injection of 1,2,5,6-dibenzanthracene as are the animals maintained under normal conditions. The present report also supports the view that no external adjuncts, such as atmospheric dust, appear to be needed in the production of pulmonary tumors in mice with carcinogenic agents. Whether the action of carcinogens, such as 20-methylcholanthrene, is a general one, producing tumors secondary to some alteration in the whole organism, or whether its action is a local one upon the tissues at the site of application, remains one of the most important undetermined questions. The present available evidence, however, points toward local action in the induction of pulmonary tumors. After the subcutaneous injection of 1,2,5,6-dibenzanthracene the absorption spectrum fails to reveal the presence of the compound in the lungs, although pulmonary tumors are induced. That the agent or some active derivative does reach the lungs, however, is suggested by the presence of photodynamic activity of emulsions of the lungs of mice injected subcutaneously with 3,4-benzpyrene.

The increase in the incidence of bronchogenic pulmonary carcinoma in man has attracted the attention of oncologists and public health officials. One of the theories presented is that the stimulus for its occurrence may be found in the atmospheric dust particles introduced into the lungs. Passey in 1922 demonstrated the presence of compounds carcinogenic to mice in the soot of soft coal discharged into the air. Campbell established that there was a marked increase in the incidence of primary pulmonary tumors in mice exposed to the dust of tarred roads. The presence of active

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carcinogens in the atmospheric dust may be of public health significance and deserves systematic investigation and attention. This report indicates the biologic testing which may be applied for the project: (1) The subcutaneous injection into male mice of strain C₃H of benzene and other extracts of dusts gathered in various localities: and (2) the intravenous injection of the unextracted dusts into mice of strain A. It must be remembered, however, that experiments on mice should not be applied, except as leads for further investigations, to other species of animals, including man. Thus, 1,2,5,6-dibenzanthracene in 0.1 mg. intratracheal doses induced pulmonary tumors in strain A mice, the introduction of much larger amounts into the trachea of rats failed to produce tumors of the lung in these animals. The only authoritative reports of the induction of pulmonary neoplasms in man by means of inhaled dust are those of the Schneeberg and Joachimstahl miners who were exposed to radioactive ores. Whether substances which are carcinogenic to mice are also carcinogenic to man, and in what doses and under what conditions, is a matter of conjecture. The pulmonary tumors in mice are similar to the pulmonary neoplasms of man in that both are found in the lungs. But, whereas the human neoplasm is believed to be almost exclusively a bronchogenic carcinoma, the mouse tumor is an adenoma or adenocarcinoma arising from the alveolar wall lining, and quite different in its development, site, and biology.

Summary. The single intravenous injection of 5 mg. of arsenopyrite, chromite, or thorite, or of 1 mg. of quartz ore (particle size 1.6 to 3.5 micra) did not induce primary pulmonary tumors in strain A mice within 6 months after the administration, despite the presence of chronic irritation. The intravenous injection of these ores did not increase the number of primary pulmonary tumors, nor did it apparently have any other effect upon the development of such tumors following the intravenous administration of 0.1 mg. of 20-methyl-cholanthrene. Soot from a chimney burning soft coal contains a benzene-soluble compound capable of initiating subcutaneous sarcoma and primary pulmonary tumors in strain C₃H male mice. The single intravenous injection of 2.5 mg. of the unextracted soot increased the incidence of primary pulmonary tumors in strain A mice." pages 251-253, (4086)

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(4119) Andervont: hepatic changes and pulmonary tumors after subcutaneous injection of 3,4,5,6-dibenzcarbazole in different strains of mice.

(4155) Lorenz & Shimkin: latent period following injection of methylcholanthrene and appearance of pulmonary tumors.

"Rate of disappearance of methylcholanthrene from lungs and body did not explain the marked difference in susceptibility of two strains of mice to induced pulmonary tumors. It therefore seems probable that pulmonary tumors arise long after the introduction of the stimulus and long after the removal of the stimulus from the body." page 497, (4155)

(4260) Shimkin & Lorenz: injection experiments suggest mode of action of pulmonary carcinogens, particularly of methylcholanthrene.

"1. Intravenous injection of methylcholanthrene dispersions in which the particles are 10μ to 20μ in size induce at least 10 times as many pulmonary tumors in strain A mice as similar dispersions in which the particles measure 1μ to 2μ . The neoplastic reaction depends upon the actual amount of the hydrocarbon that lodges in the lungs and not upon the amount injected into the organism. This is evidence supporting the view that the pulmonary tumor reaction is a local one of the hydrocarbon upon the susceptible pulmonary tissue rather than a general systemic effect. 2. The lungs of young, small strain A mice are more susceptible to the induction of pulmonary tumors with intravenous dibenzanthracene than the lungs of old, large mice of the same strain. The amount of hydrocarbon retained in the lungs is the same in both cases, but the smaller lungs of the young mice permit a higher concentration of the hydrocarbon in the tissue." page 509, (4260)

(4323) Bryan & Shimkin: dose-response data obtained with three carcinogenic hydrocarbons in strain C₃H male mice.

(4414) Andervont: occurrence of mammary tumors in mice influenced by segregation.

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(4964) Shimkin & McClelland: statistical analysis of data on the induction of pulmonary tumors in strain A mice following intravenous injection of methylcholanthrene.

(4968) Stewart: review research on carcinogenic agents in progress at the National Cancer Institute:

"In summary, a few of the uses being made of carcinogenic agents in work now going on at the National Cancer Institute have been described. By means of these substances we hope to be able to identify the factor or factors which may be essential in the production of neoplasms, and also to determine what the earliest stages of cancer look like, so that neoplastic disease may be detectable in a curable stage. Finally, we hope some day to ascertain the underlying characteristics which are peculiar to cancer cells. This calls for the collaboration of all the medical sciences, as well as the disciplines of physics, biochemistry, radiology, nutrition and others. Only by such an all-out attack will the nature and origin of cancer be determined. It can be seen that the problem of tumor induction by carcinogenic agents touches the very core of the problems of growth and life." page 1096, (4968)

Cancer research laboratories in the United States. The research activities conducted at private institutions were less extensive than those at the National Cancer Institute. The following list includes research topics relating to environmental factors in dermal carcinogenesis.

(4054) Law; Jackson Memorial Laboratory, Bar Harbor, ME: amniotic fluid injection of 1:2:5:6-dibenzanthracene in mice.

(4092) Syverton & Berry; University of Rochester, NY: sarcomata and carcinomata induced by methylcholanthrene in cottontail rabbits.

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(4230) Green; Bryn Mawr College, PA: crystalline material in lung tissue of mice after subcutaneous injection of 1:2:5:6-dibenzanthracene.

(4424) Carruthers & Santzeff; Washington University School of Medicine, St. Louis, MO: chemical studies on transformation of mouse epidermis by methylcholanthrene.

(4427) Cowdry & Suntzeff; Washington University, St. Louis, MO: tumors induced by methylcholanthrene appeared more quickly and in a higher percentage of young than in old mice.

(4437) Friedewald & Rous; Rockefeller Institute for Medical Research, New York, NY: benzpyrene brought about neoplastic changes in rabbit epidermis; there was no reference to publications by Roffo among 34 citations.

(4471) Silberberg & Silberberg; New York University College of Medicine, NY: benzpyrene applied to skin of mice accelerated wound healing.

(4471) Silberberg & Silberberg; New York University College of Medicine: benzpyrene effect was slower than that of benzene.

(4518) Cowdry; Washington University, St. Louis, MO: epidermal carcinogenesis after methylcholanthrene in mice.

(4572) Simpson & Cramer; Washington University, St. Louis, MO: methylcholanthrene dissolved in lanolin was rendered inactive on mouse skin.

(4618) Dunlap & Warren; Harvard Medical School, MA: derivatives of benzanthrane tested for carcinogenic activity in mice.

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(4657) Silberberg & Silberberg; Jewish Hospital, St. Louis, MO: inhibition of wound epithelization in mice treated with benzpyrene or methylcholanthrene.

(4659) Stowell & Maas; Washington University, St. Louis, MO: large doses of methylcholanthrene painted on skin caused systemic effects in mice.

(4660) Strong; Yale University School of Medicine, New Haven, CT: hybrid mice resulted in resistance to induced tumor by methylcholanthrene.

(4661) Strong; Yale University School of Medicine, New Haven, CT: genetic principles that control cancer.

(4726) Cowdry; Washington University, St. Louis, MO: epidermal carcinogenesis and hypersensitivity.

(4891) Thomas & Stetson; Johns Hopkins University, Baltimore, MD: Schwartzman phenomenon from topical application of bromobenzene.

Chester Beatty Research Institute, Cancer Hospital (Free), London, GBR. Kennaway & Kennaway and their collaborators pioneered in the identification of carcinogens in coal tar and related fossil fuel products. They were also credited for the combined use of chemical analysis, isolation, synthesis, and biologic testing in the identification of four reference compounds, namely, dibenzanthracene, benzanthracene, benzopyrene, and methylcholanthrene. Their publications relating to

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experimental skin cancer in mice are listed below in chronological sequence starting in the early 1930's.

(3233) Cook, Hieger, Kennaway & Maynoerd: testing for cancer producing action of polycyclic aromatic hydrocarbons.

(3333) Cook, Hewett & Hieger: isolation of benzopyrene from coal tar.

(3544) Barry, Cook, Haslewood, Hewett, Hieger & Kennaway: testing of tetracyclic and pentacyclic aromatic hydrocarbons.

(3740) Bachman, Cook, Dansi, de Worms, Haslewood, Hewett & Robinson: testing in mice and rats of about 140 compounds.

(3741) Cook, Haslewood, Hewett, Hieger, Kennaway & Mayneord: test of cholanthrene derivatives.

(4022) Badger, Cook, Hewett, Kennaway, Kennaway, Martin & Robinson: testing of 70 additional compounds.

(4515) Burrows, Roe & Schober: electrical action potential differences in skin of mice during carcinogenesis.

(4942) Hieger: review of chemical carcinogenesis.

During the late 1940's, scientists at the Chester Beatty Research Institute turned their interest to carcinogenic compounds not present in coal tar, as well as anti-cancer agents (see Topic E).

Other cancer research laboratories in Great Britain. The most significant contributions from British academic institutions are listed below. Details on "cocarcinogenic action" on mouse skin were reported for the first time.

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(4123) Berenblum; Oxford University Centre of British
Empire Cancer Campaign:

"The effect of croton resin on carcinogenesis was studied under varying conditions, in order to determine the nature of cocarcinogenic action (the argumentation of carcinogenesis which occurs when croton resin is applied to the skin concurrently with a dilute solution of 3,4-benzpyrene) and its relation to the normal process of carcinogenesis. No cocarcinogenic effect was observed when the croton resin was applied to the skin and the benzpyrene was injected at a distance (intra-peritoneally); nor was it possible to augment the carcinogenic effect of benzpyrene on subcutaneous tissues, by injection of croton resin together with the benzpyrene. While augmentation of carcinogenesis was very pronounced when croton resin was applied to the skin concurrently with a dilute solution of a potent carcinogen (3,4-benzpyrene), none was observed with concentrated solutions of different carcinogens, irrespective of whether their potency were high (3,4-benzpyrene), moderate (1,2,5,6-dibenzanthracene), or very low (1,2-benzanthracene). Preliminary treatment with croton resin for a period of 26 weeks failed to influence significantly the response of the mouse's skin to subsequent applications of benzpyrene. On the other hand, croton resin applied to the skin subsequent to a limited period of benzpyrene treatment led to a striking increase in the development of tumors. Croton resin applied to papillomas already established appeared to facilitate their conversion to malignancy. From consideration of these results, the suggestion is put forward that the three phases of carcinogenesis - (a) the development of the preneoplastic phase (latent period), or precarcinogenic action, (b) the conversion of this into the wart stage, or epicarcinogenic action, and (c) the malignant transformation of these warts, or metacarcinogenic action - are probably not simply stages of one single carcinogenic process, but independent processes. The carcinogenic hydrocarbons possess all three actions; croton resin possesses only the second and third, and cannot, therefore, produce tumors by itself. No precise knowledge is yet available as to the nature of cocarcinogenic action, but two possible modes of actions are discussed.

The most significant experiment was that in which the croton resin was applied to the skin in conjunction with 1,2,5,6-dibenzanthracene and 1,2-benzanthracene respectively, and, apart from the conclusions which have

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already been reached from this experiment, the results also help to throw a little light on the mechanism of cocarcinogenesis. The simplest conception of cocarcinogenic action would be that it was merely a variant of epicarcinogenic action, on the supposition that the dilute benzpyrene produced the preneoplastic state, while the epicarcinogenic effect was carried out jointly by the dilute benzpyrene and the croton resin. If this were the case, one would have to assume, first, that the precarcinogenic action of benzpyrene is less influenced by dilution than its epicarcinogenic action and, second, that the low carcinogenic potency of dibenzanthracene and the still lower potency of benzanthracene are due primarily to deficiencies in precarcinogenic action. Until these assumptions are confirmed experimentally it is not possible to say whether this simple explanation of cocarcinogenic action is correct or not. An entirely different explanation of the mode of action of cocarcinogenesis would be to suppose that croton resin merely facilitated the entry of the carcinogen into the cell so that a small number of molecules of the hydrocarbon, applied to the surface, would still have a reasonable chance of acting on the cell. This would account for the failure of croton resin to augment carcinogenesis in the case of concentrated solutions of carcinogens, irrespective of whether their potencies are high, medium, or low. This interpretation implies, however, that cocarcinogenic action is an entirely different process from pre-, epi-, and meta-carcinogenic action. No decision can be made at the present stage as to the likelihood of this explanation being the right one." pages 813-814, (4123)

(4416) Berenblum; University of Oxford, GBR:

"Many books and reviews and innumerable other publications have appeared from time to time with the set purpose of finding a solution to the problem of the part played by irritation in the development of a tumor. Some of these publications are noteworthy for the patience and the care displayed by the authors in searching through the literature for all references that may have any bearing on the problem. Unfortunately, such reviews commonly suffer from insufficient critical judgment, whether dealing with mere expressions of opinion, with casual observations or with detailed results obtained from statistical analyses. Some publications place critical judgment in the forefront of the work, but among these the 'judgment' is sometimes carried too far, tending toward irrational skepticism.

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Publications confined to statistical analyses are more useful, provided the nature of the irritant is carefully specified in every case and other postulates are rigidly applied. But most publications are concerned with a few cases personally observed by the authors and with such citations from the literature as happen to support the particular thesis they wish to stress. Perhaps the fault of the majority of publications on the subject lies in the fact that the question posed - Is irritation the cause of tumor formation? - is too simple. The result of such an inquiry tends to resolve itself into a statement as to how many authorities are for this view and how many are against. Unfortunately, decision by majority is not the best means of establishing scientific truth.

The evidence indicates that preneoplastic hyperplasia is a highly specific type of hyperplasia since only carcinogenic irritant can produce with certainty, but that once the preneoplastic state has been induced (by a true carcinogen) a benign tumor can be made to appear at that site and a tumor already present can have its progress to carcinoma hastened, by the action of a variety of noncarcinogenic irritants. If this is confirmed, the following practical lessons will have been learned: (a) that there is little danger of an ordinary irritant producing a tumor of its own accord; (b) that this applies also to the initiation of a preneoplastic lesion; (c) that, given a preneoplastic lesion, the subsequent development of a benign tumor at the site may be facilitated, and its progress to cancer hastened, by the action of a variety of nonspecific irritants. It is a comforting thought, however, that with most nonspecific irritants this facilitation is far less effective than it is with a true carcinogen." pages 243-244, (4416)

(4417) Berenblum & Schoental; University of Oxford, GBR:

"A sample of blue shale oil was found to be strongly carcinogenic to the mouse's skin, whereas a concentrated extract of shale (the natural product from which shale oil is obtained by retorting) failed to produce any tumours after 40 weeks of painting. These results confirm the view, previously expressed by the authors, on the evidence of fluorescence analysis of chromatographic fractions of shale oil and extract of shale, that the carcinogenic constituents of shale oil do not exist in the original shale, but owe their presence to pyrolytic effects during the retorting." page 96, (4417)

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(4428) Crabtree; Imperial Cancer Research Fund, Mill Hill, London, GBR: carcinogenic action of 3,4-benzpyrene on mouse skin was inhibited and sometimes prevented by local application of bromobenzene.

(4519) Crabtree; Imperial Cancer Research Fund, Mill Hill, London, GBR: carcinogenic action of 3,4-benzpyrene and 1,2,5,6-dibenzanthracene on mouse skin was greatly retarded by maleic and citraconic anhydrides.

(4544) Lea; Strangeways Laboratory, Cambridge, GBR: mean of logarithms of induction times proposed as means of summarizing results of carcinogen assay.

(4561) Pullinger; Imperial Cancer Research Fund; multiple simple excisions from mouse skin treated with benzpyrene stimulated tumor formation.

(4564) Riley & Pettigrew; Wilkie Surgical Research Laboratory, University of Edinburgh, GBR: mechanical irritation caused accelerated carcinogenesis in skin of mice painted with 1:2:5:6-dibenzanthracene.

(4611) Armstrong & Bonser; University of Leeds, GBR: retesting of mice sensitive to benzpyrene.

(4617) Dickens & Weil-Malherbe; North England Council of the British Empire Cancer Campaign, Newcastle-upon-Tyne, GBR: anticarcinogenic action in certain samples of mouse fat is due neither to content of unsaturated fatty acids nor of saturated

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one. Rate of elimination of benzpyrene bore no relationship to carcinogenic nature of solvent.

(4639) Irwin & Goodman; Medical Research Council, London, GBR: statistical treatment of carcinogenic properties of tars and mineral oils conducted by Twort & Twort on mice.

(4665) Weil-Malherbe & Dickens; Newcastle-upon-Tyne, GBR: influence of cholesterol and phospholipids on tumorigenic effects of benzpyrene injected subcutaneously in mice.

(4711) Anderson; London, GBR: physico-chemical aspects of chemical carcinogenesis.

(4715) Berenblum; Oxford University Research Centre of the British Empire Cancer Campaign: analysis of cocarcinogenesis from results of Berenblum, of Rouse and his associates, and of Mottram. Note that concept of cocarcinogenesis was derived from skin painting studies.

(4716) Berenblum & Schoental; University of Oxford, GBR. Further attempts to understand mechanism of carcinogenesis in experimental skin painting in mice:

"1. In order to study the stages of carcinogenesis by quantitative means, use was made of the technique, based on Mottram's work, whereby tumours of the mouse's skin may be induced by a single application of a carcinogen, followed by repeated applications of croton oil. 2. When the croton oil treatment was kept constant but different carcinogens were used for the initial painting, the tumour incidence varied from group to group but the average latent period remained the same. 3. When the initial painting with the carcinogen was kept constant but the croton oil treatment was delayed, the tumour incidence remained the same but the latent period varied, corresponding approximately to the lengths of the intervals free from treatment. 4. It was

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concluded that the initial action in carcinogenesis constitutes a sudden and irreversible process, whereby a few normal cells are changed into permanently altered 'latent tumour cells,' which lie dormant among the non-neoplastic cells. The mechanism by which these latent tumour cells are made to develop into tumours is altogether different from that of the initial transformation." page 164, (4716)

(4717) Berenblum & Shubik; University of Oxford, GBR

"A carcinogenic tar was fractionated by (1) extraction with solvents, (2) chromatography on alumina columns, (3) high vacuum distillation, and (4) crystallization, formation of picrates, etc. The fractions were tested for carcinogenic activity, by skin painting in mice and rabbits, and for benzpyrene content, by fluorescence spectrography." page 390, (4717)

(4722) Calcutt & Powell; Radium Institute, Northwood, Middlesex, GBR: clipping of fur is best preparation of skin; mice very rapidly lick off any reagent applied to skin.

(4730) Dickens; Courtauld Institute of Biochemistry, Middlesex Hospital Medical School, London, GBR: influence of nature of solvent on carcinogenic response of 3,4-benzpyrene in mice.

(4789) Weil-Malherbe; King's College Medical School, Newcastle-upon-Tyne, GBR: effect of lipid solvents on rate of elimination and the carcinogenic potency of 3,4-benzpyrene after subcutaneous injection in mice.

(4790) Weil-Malherbe; Newcastle-upon-Tyne, GBR: elimination and carcinogenic potency after subcutaneous injection in nonlipoid solution.

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(4812) Badger; University of Glasgow, GBR: chemical structure and carcinogenic activity; review of 20 years research on polycyclic aromatic hydrocarbons.

Co-carcinogenicity of wood soot. Sulman & Sulman, from the Hebrew University in Jerusalem, collected the soot from the chimney of a smoked sausage factory. The results from experiments on rats were as follows:

"Thirty-six female rats implanted subcutaneously with fragments of soot from the chimney of a sausage factory developed sarcoma in 16.6 per cent of the cases. No tumor developed in 36 male rats implanted intrascrotally with bits of the same soot. Ten female mice treated for 2 years with an ether and alcohol extract of wood soot showed tumor formation in 3 cases (2 sarcomas and 1 carcinoma). Twenty rats fed for 2 years on a diet containing an unlimited amount of smoke sausage failed to develop tumors. The conflicting finding, carcinogenic effect in parenteral treatment versus absence of carcinogenic effect after oral administration, indicates the need for further study of the carcinogenic activity of smoked food, in view of the practical importance of the problem for human nutrition. The consumption of smoked sausage over a period of more than 2 years did not cause tumors in rats. However, the wood smoke used for its preparation was shown to contain substances that were carcinogenic for rats when introduced subcutaneously, and for mice when rubbed into the skin. The sarcomas obtained in 16.6 per cent of the rats following the implantation of soot particles may not appear significant, in view of the finding by Turner that sterile bakelite disks, when similarly implanted in rats, elicited sarcomas in 31 per cent of the animals. Our finding became significant, however, by reason of the carcinogenicity of the soot extracts for mice (33.3 per cent) when rubbed into the skin. A further study of the possible carcinogenic role of wood soot extracts therefore seems desirable." page 367, (4663)

Like all other skin painting experiments, the above on soot extracts with positive results were not applied to speculate on

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